CHRONIC TOXICITY SUMMARY

DIETHANOLAMINE

(DEA; 2,2'-iminodiethanol; 2,2'-iminobisethanol; diethylolamine; 2,2'-aminodiethanol; 2,2'-dihydroxydiethylamine)

CAS Registry Number: 111-42-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**3 µg/m^3** (0.6 ppb)
Critical effect(s)	Laryngeal lesions in rats
Hazard index target(s)	Respiratory system; cardiovascular system

II. Physical and Chemical Properties (Melnick and Thomaszewski, 1990; Dow, 1980; CRC, 1994)

Description	Colorless crystals
Molecular formula	$C_4H_{11}NO_2$
Molecular weight	105.14 g/mol
Density	1.097 g/cm^3 @ 20°C
Boiling point	268.8°C
Melting point	28°C
Vapor pressure	0.00014 torr @ 25°C
Solubility	Soluble in alcohol, water, acetone
Conversion factor	1 ppm = 4.3 mg/m^3 @ 25°C

III. Major Uses and Sources

Diethanolamine is used in the formation of soaps, emulsifiers, thickeners, wetting agents, and detergents in cosmetic formulations (Melnick and Thomaszewski, 1990; Knaak *et al*., 1997). It is used as a dispersing agent in some agricultural chemicals, as an absorbent for acidic gases, as a humectant, as an intermediate in the synthesis of morpholine, as a corrosion inhibitor, and as a component in textile specialty agents (Beyer *et al*., 1983). Diethanolamine is permitted in articles intended for use in production, processing, or packaging of food (CFR, 1981; cited in Melnick and Thomaszewski, 1990). It is also found in adhesives, sealants, and cutting fluids (Melnick and Thomaszewski, 1990). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1520 pounds of diethanolamine (CARB, 2000).

IV. Effects of Chronic Exposures to Humans

There have been no controlled or epidemiological studies of chronic diethanolamine exposure in humans. There is a single case report of occupational asthma determined to be due to the patient's handling of a cutting fluid containing diethanolamine (Piipari *et al*., 1998). Specific bronchial provocation tests were done with the cutting fluid containing DEA and with DEA aerosol at two concentrations (0.75 mg/m^3 and 1.0 mg/m^3) below the occupational limit of 2.0 mg/m^3. DEA caused asthmatic airway obstruction at both concentrations, but IgE-antibodies specific for DEA were not found.

V. Effects of Exposures in Animals

Diethanolamine replaces choline in phospholipids (Blum *et al.*, 1972). DEA also reversibly inhibits phosphatidylcholine synthesis by blocking choline uptake and competing for utilization in the CDP-choline pathway (Lehman-McKeeman and Gamsky, 1999). Systemic toxicity occurs in many tissue types including the nervous system, liver, kidney, and blood system.

Gamer *et al*. (1996*)* exposed groups of 26 Wistar rats (13 male and 13 female) head-nose to a liquid aerosol of DEA for six hours per working day for 90 days at target concentrations of 15, 150, and 400 mg/m^3. Three of each sex were used for whole animal perfusion studies and the remaining 20 animals were examined for pathology. The study found no functional or morphological evidence of neurotoxicity. Retardation of body weight increase was observed in animals exposed to high concentrations. No systemic effects occurred at the low dose, but systemic effects in the liver, kidney, male reproductive system, and red blood cell occurred in the high concentration dose group. In the mid-dose group, mild liver and kidney effects were present. Local irritation of the larynx and trachea was found in the high and mid dose groups; irritating laryngeal effects were also detected in the low dose group. Based on this study 15 mg/m^3 is a NOAEL for liver and kidney effects and a LOAEL for irritation of the larynx. The equivalent continuous exposure at the LOAEL is 2.7 mg/m^3 (15 x 6/24 x 5/7).

Incidence of laryngeal lesions (Gamer *et al*., 1996)

Aerosolized diethanolamine	Chronic inflammation of the larynx	Squamous hyperplasia	Focal squamous metaplasia of laryngeal epithelium at base of the epiglottis
0	None*	None	None
15 mg/m^3	4/20	0/20	20/20
150 mg/m^3	20/20	13/20	20/20
400 mg/m^3	20/20	17/20	20/20

* The report does not give control incidences. Assumed 0/20.

In an abstract Hartung *et al*. (1970) reported that inhalation by male rats of 6 ppm (25.8 mg/m^3) DEA vapor 8 hours/day, 5 days/week for 13 weeks resulted in depressed growth rates, increased lung and kidney weights, and even some mortality. Rats exposed continuously for 216 hours (nine days) to 25 ppm (108 mg/m^3) DEA showed increased liver and kidney weights, elevated

blood urea nitrogen (BUN), and increased serum glutamate oxaloacetate transferase (SGOT), an indicator of liver damage (Hartung et al., 1970). In studies at lower DEA levels, Eastman Kodak (1967) exposed dogs, weanling and adult rats, and guinea pigs to 0.26 ppm (1.1 mg/m^3) DEA for 90 days and found no pathology attributable to DEA. In a 45-day study with 0.5 ppm (2.2 mg/m^3) DEA they also found no pathology attributable to DEA except for a possible slight retardation in rat growth rate.

Gamer *et al*. (1993) exposed groups of 25 pregnant Wistar rats on gestation days 6-15 to a (nose-only) liquid aerosol of DEA at 10, 50 and 200 mg/m^3. Maternal toxicity, indicated by vaginal hemorrhage in 8 of the dams on gestation day 14, and fetotoxicity, evidenced by a statistically significant ($p<0.05$) increased incidence of total fetal skeletal variations, were observed at 200 mg/m^3. No teratogenic effects were seen at any level. Thus 50 mg/m^3 was a NOAEL for maternal toxicity and for embryo-fetal effects.

A 13-week drinking water study in rats (10 per sex per group) showed significant dose-dependent hematological changes following exposure to DEA at all concentrations tested: 320, 630, 1250, 2500, and 5000 ppm in males, and 160, 320, 630, 1250, and 2500 ppm in females. Hematological effects included decreased hemoglobin and mean corpuscular volume (Melnick *et al.*, 1994a). Similar hematological changes were observed following daily topical treatment. In addition to the hematological effects, female rats also showed dose-dependent spinal cord and medullary demyelination beginning at a drinking water concentration of 1250 ppm DEA. Male rats displayed demyelination beginning at 2500 ppm. Female rats gained significantly less weight than controls beginning at 63 mg/kg/day topical treatment. In a companion drinking water study (Melnick *et al.*, 1994b), mice (10 per sex per group) were exposed to concentrations of 0, 630, 1250, 2500, 5000, and 10,000 ppm DEA and displayed dose-dependent hepatotoxicity, nephrotoxicity, and cardiac toxicity. Daily topical treatment in a separate study resulted in skin lesions in mice. Significant hepatic toxicity was observed at all drinking water concentrations, and skin lesions were observed at all topical doses.

Data from female rats exposed to diethanolamine by Melnick *et al*. (1994)

Dose (ppm)	mg/kg/day DEA consumed	Survival	Mean bw change (g)	Hgb (g/dL)	Mean cell volume	Mean cell Hgb (pg)
0	0	10/10	120±6[a]	15.1±0.3	56±0.2	17.9±0.2
160	14	9/10	106±3	15.2±0.1	55±0.2**	17.8±0.1*
320	32	10/10	98±3**	13.8±0.1**	54±0.2**	17.7±0.1**
630	57	10/10	95±4**	13.0±0.1**	53±0.3**	17.2±0.1**
1250	124	10/10	85±4**	11.3±0.2**	51±0.3**	16.7±0.1**
2500	242	10/10	63±4**	10.50±.2**	49±0.2**	16.30±.1**

[a] Values are means±SEM; * $p<0.05$ or ** $p<0.01$ versus control group

Barbee and Hartung (1979a) found that repeated treatment of rats with 330 mg DEA/kg/day significantly inhibited formation of phosphatidyl choline and phosphatidyl ethanolamine in the liver as compared with control rats. In a subsequent study, Barbee and Hartung (1979b) noted changes in liver mitochondrial activity in rats (4 per group) following exposure to DEA in

drinking water for up to 5 weeks. Mitochondrial changes were observed at 42 mg/kg/day after 2 weeks.

Daily oral treatment of male rats with 0, 250, 500, or 750 mg/kg/day for 5 days, or 100 mg/kg/day for 14 days resulted in reduced activities of the liver enzymes microsomal hydroxylase and N-demethylase (Foster *et al.*, 1971).

In a developmental study Marty *et al.* (1999) administered DEA cutaneously to pregnant CD rats during gestation days 6-15 at doses of 0, 150, 500, and 1500 mg/kg/day. Dams exhibited reduced body weight at the highest dose, skin irritation and increased kidney weights at both 500 and 1500 mg/kg/day, and a slight microcytic anemia with abnormal red blood cell morphology at all 3 dose levels. The blood results are consistent with the results of topical application of DEA by Melnick *et al*. (1994b). Rat fetuses had increased incidences of six skeletal variations at 1500 mg/kg/day. Lower doses were without effect on the fetuses. Marty *et al*. (1999) also administered DEA cutaneously to pregnant New Zealand White rabbits on days 6-18 of gestation at 0, 35, 100, and 350 mg/kg/day. Dams administered the highest dose exhibited various skin lesions, reduced food consumption, and color changes in the kidneys, but no hematological changes. Body weight gain was reduced at ≥ 100 mg/kg/day. There was no evidence of maternal toxicity at 35 mg/kg/day and no evidence of developmental toxicity in rabbits at any dose. Developmental toxicity was observed only in the rat and only at doses causing significant maternal toxicity, including hematological effects. Due to a dose discrepancy, the authors adjusted the no observable effect level (NOEL) for DEA developmental toxicity to 380 mg/kg/day for rats. In rabbits, the embryonal/fetal NOEL was 350 mg/kg/day.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Gamer *et al*. (1996)
Study population	Wistar rats (male and female)
Exposure method	Inhalation 6 h/day, 5 d/wk
Critical effects	Chronic inflammation and squamous hyperplasia and metaplasia of the larynx
LOAEL	15 mg/m^3
NOAEL	Not observed
Exposure duration	90 days
Average experimental exposure	2700 $\mu g/m^3$ for LOAEL group (15 mg/m^3 x 6h/24h x 5d/7d x 1000 $\mu g/mg$)
LOAEL uncertainty factor	3 (see below)
Subchronic uncertainty factor	3
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	3 $\mu g/m^3$ (0.6 ppb)

No chronic inhalation studies with diethanolamine were located in the peer-reviewed literature. Thus the 90 day study by Gamer *et al*., which found a LOAEL of 15 mg/m^3 for irritation of the

rat larynx, was used to derive the REL. All 20 of the rats in the 15 mg/m^3 exposure group showed focal squamous metaplasia of the laryngeal epithelium at the base of the epiglottis, and 4 of the 20 had inflammatory cells present in the larynx. The former lesion seemed to be very limited and did not justify use of the full LOAEL uncertainty factor of 10.

For comparison, the BASF (1993) developmental study by the inhalation route found a LOAEL of 200 mg/m^3 DEA and a NOAEL of 50 mg/m^3 for fetotoxic effects. The equivalent continuous exposure at the NOAEL is 12.5 mg/m^3. Multiplying by an RGDR of 1 and dividing by an interspecies uncertainty factor (UF_A) of 3 and an intraspecies uncertainty factor (UF_H) of 10 results in a REL estimate of 40 µg/m^3.

As another comparison, the study by Melnick *et al.* (1994a) shows dose-dependent adverse hematological and CNS effects in rats exposed to DEA in drinking water. Similar systemic effects were observed following dermal exposure. The Melnick *et al.* subchronic study was of the longest duration and was the most comprehensive report of the systemic effects of DEA in the literature. However, portal-of-entry effects of DEA have not been examined and should be addressed in future studies since this compound has irritant properties. The data from female rats were used since females were more sensitive than males to the hematologic effects of DEA. The LOAEL was 160 mg/L, or 14 mg/kg-day based on water consumption rates. Dividing by a LOAEL UF of 3, a subchronic UF of 3, an interspecies UF of 10, and an intraspecies UF of 10 (cumulative UF = 1000) results in a oral REL of 0.014 mg/kg-day. Using route-to-route extrapolation and assuming that a 70 kg person inhales 20 m^3 of air per day leads to an inhalation REL estimate of 50 µg/m^3 (10 ppb) DEA.

VII. Data Strengths and Limitations for Development of the REL

The diethanolamine database is relatively weak. Major areas of uncertainty are the lack of adequate human exposure data, the absence of a NOAEL in the major study, the lack of reproductive and developmental toxicity studies, and the lack of chronic inhalation, multiple-species, health effects data.

VIII. Potential for Differential Impacts on Children's Health

Since the proposed chronic REL of 3 µg/m^3 based on laryngeal effects is much lower than the comparison REL of 40 µg/m^3 based on fetotoxic effects, the REL should adequately protect infants and children. Diethanolamine is a respiratory irritant and thus might exacerbate asthma, which has a more severe impact on children than on adults. The large uncertainty factor of 1000 should protect against that potential hazard. However, there is no direct evidence in the literature to demonstrate that DEA exacerbates asthma or to quantify a differential effect of diethanolamine on the larynx or on other organs in infants and children.

IX. References

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